Vaccine 36 (2018) 7956–7964

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Spontaneous reports of vaccination errors in the European regulatory database EudraVigilance: A descriptive study

Christina E. Hoeve [a,b,*], Anja van Haren [a], Miriam C.J.M. Sturkenboom [c], Sabine M.J.M. Straus [a,b]

[a] Medicines Evaluation Board, Utrecht, the Netherlands
[b] Erasmus University Medical Center, Rotterdam, the Netherlands
[c] University Medical Center, Utrecht, the Netherlands

ARTICLE INFO

Article history:
Received 4 August 2018
Received in revised form 30 October 2018
Accepted 1 November 2018
Available online 8 November 2018

Keywords:
Spontaneous reporting
Medication errors
Vaccination errors
EudraVigilance
Pharmacovigilance

ABSTRACT

Background: Among all post-marketing medication error reports submitted to EudraVigilance, vaccines are the most frequently reported medicinal products. This study aims to describe the characteristics of vaccination errors submitted to Eudravigilance between 2001 and 2016.
Methods: EudraVigilance is a spontaneous reporting database for adverse events maintained by the European Medicines Agency. We extracted Individual Case Safety Reports (ICSRs) submitted to EudraVigilance between 1 January 2001 and 31 December 2016. Reports were included for analysis if a vaccine was reported as interacting or suspect drug and at least one medication error term was listed as an adverse reaction. ICSRs were stratified by age and gender, by year of reporting, region of origin, reporter profession, seriousness of outcome, ATC, and type of error.
Results: In total, 7097 ICSRs were included in the study. We observed a yearly increase in the reporting of vaccination errors, with the proportion to all vaccine ICSRs increasing from 0.4% to 4.0% between 2001 and 2016. The majority of reports was classified as serious (4248, 59.9%), but non-serious reports were increasingly reported since 2012. The mean age of patients was 24.1 years. The most frequently reported vaccines were influenza (13.5%), bacterial and viral combined (12.3%), and hepatitis vaccines (11.8%). A total of 8167 medication error terms were reported. The most frequently reported terms were "Inappropriate schedule of drug administration" (27.2%), "Incorrect route of drug administration" (12.5%) and "Drug administered to patient of inappropriate age" (10.0%). For infants and children, the error "Drug administered to patient of inappropriate age" was reported more often than for all other age categories.
Discussion: Vaccination errors are increasingly submitted to EudraVigilance. Errors related to the schedule are the most common errors reported with vaccines. However, consequences of vaccination errors appear to be relatively mild.

1. Introduction

In the EU, all adverse event reports are collected and shared in EudraVigilance, a European wide pharmacovigilance database [1,2]. Since July 2012 the EU pharmacovigilance legislation provides a legal framework to share data on medication errors, in which medication errors are defined as "an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient" [1,3]. The definition of medication errors in this legislation does not include 'intended errors' such as off-label use, misuse and abuse [3]. In EudraVigilance, vaccines are the most frequently reported medicinal group among medication errors cases in EU countries [4]. Several studies have reported

Abbreviations: VAERS, Vaccine Adverse Event Reporting System; HCP, Healthcare Professional; NCA, National Competent Authority; MAH, Marketing Application Holder; ICSR, Individual Case Safety Report; ATC, Anatomical Therapeutic Classification; MedDRA, Medical Dictionary for Regulatory Activities; SMQN, Narrow Standard MedDRA Query; PT, Preferred Term; ICH, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; SmPC, Summary of Product Characteristics; HPV, Human Papilloma Virus; HiB, Haemophilus influenza B.

* Corresponding author at: Erasmus University Medical Center, Rotterdam, the Netherlands.
E-mail address: c.hoeve@erasmusmc.nl (C.E. Hoeve).

https://doi.org/10.1016/j.vaccine.2018.11.003
0264-410X/

data on vaccination errors, although the majority of these originated from US reporting systems [5–14]. Although in some cases vaccination errors may leave the patient unprotected against disease [15,16], vaccination errors do not necessarily cause injury. Above mentioned studies in Vaccine Adverse Event Reporting System (VAERS) show that in general vaccination errors result in little harm. Studies have shown that the reporting of vaccination errors has increased in the past decade in the USA, which may be explained by several reasons such as changes in reporting practices, the increasing number of vaccines in the national immunization program, and increased awareness of the importance of reporting medical errors [12,17].

Specific pharmacovigilance guidance has been developed for vaccines as these have a specific position in the spectrum of medicinal products. In contrast to most regular medications, vaccines are used to prevent rather than cure diseases and are used in relatively healthy populations. As a result, fewer risks are tolerated with the use of vaccines. Vaccines are often administered to large populations as part of public health programs. Moreover, specific storage requirements apply to vaccines, and vaccination schedules may be complex and difficult to adhere to [18]. Errors may occur at any stage of the treatment process and consequences of errors associated with vaccines may be different from other medications.

The role of spontaneous reporting systems in the context of medication errors has been described for medications in general, but limited knowledge is available on vaccination errors submitted to EudraVigilance. In the current study, we aim to describe vaccination errors in EudraVigilance, to gain insight into the types of errors and to identify potential areas where preventive measures may be beneficial.

2. Methods

2.1. Study design

A descriptive case series study was performed in EudraVigilance on vaccination errors reported by a healthcare professional (HCP) or non-HCP to an EU national competent authority (NCA) or marketing application holder (MAH) in the period of 1 January 2001 through 31 December 2016. We retrieved all reports and as reference date for all analyses we used the date when an NCA or MAH received the initial report. If multiple versions of the same report were identified, only the latest version was used for further analysis. For the analysis, all Individual Case Safety Reports (ICSRs) reporting a medication error term and at least one vaccine as a suspect medication, were downloaded from the EudraVigilance Post Authorization Module. Therefore, only post-marketing ICSRs were included. All ICSRs were extracted on 11 September 2017.

2.2. ICSR extraction

Vaccines were identified by searching for active substances of vaccines using search terms such as human papilloma, herpes, influenza, et cetera. Subsequently, all drugs identified in the selected reports were classified by Anatomical Therapeutic Classification (ATC) code. Drugs with an ATC code not starting with J07 were excluded from the analysis. All adverse drug reactions and clinical terms (e.g. diagnostics) reported in the ICSRs are coded by the Medical Dictionary for Regulatory Activities (MedDRA®) terminology[1]. All ICSRs submitted within the study period were extracted using the narrow Standardised MedDRA query (SMQN) 'Medication error' from MedDRA version 20.0. This SMQN is a collection of MedDRA preferred terms (PTs) to identify medication error cases (e.g. *administration error* or *product administered to wrong patient*). All PT's listed in the SMQN were categorized into 10 error groups based on the types of errors: Accidental exposure, Administration errors, Contraindication/Warning, Dispensing/selection/prescription error, General error, Information error, Storage error or quality-related issue, Vaccination incomplete, Wrong dose, Wrong patient/drug/age (Appendix A). Reported cases in EudraVigilance are classified as serious when categorized in at least one of the following subcategories: death, life-threatening, hospitalization, disabling, congenital anomaly or other nature according to the ICH definitions [19,20].

2.3. Analysis

The reports extracted from EudraVigilance were classified by age and gender, by year and month of reporting, region of origin of the report (EU or non-EU), reporter profession (healthcare professional or non-healthcare professional), seriousness of reported outcome, ATC level 4, and PT. All countries associated with the European Medicines Agency (i.e. EU countries plus Iceland, Liechtenstein, and Norway) were classified as EU. Patients were categorized in age groups as follows: infants $0 < 2$ years, children $2 < 12$ years, adolescents $12 < 18$ years, adults $18 < 65$ years, elderly $65 < 75$ years, very elderly ≥ 75 years. Where applicable a two-sided binomial test was performed to compare proportions, with the null-hypothesis assuming that there is no difference between the proportions of the categories tested. The aim of such testing was to highlight differences in *reporting* of vaccination errors that may need further evaluation, rather than to confirm differences in the *occurrence* of vaccination errors. Data handling and analysis were performed in SAS software version 9.3 (SAS Institute Inc., USA). Missing data were considered as 'not reported' and formed an extra outcome category.

3. Results

Between 1 January 2001 and 31 December 2016, there were 233,285 vaccine reports of which 7097 (3.0%) reported a vaccination error. The number of vaccination error reports received per year increased from 5 in 2001 to 1007 in 2016 (Fig. 1). Simultaneously, the proportion of vaccination error reports among all vaccine reports increased from 0.4% to 4.0%. However, among all medication error reports in EudraVigilance, the proportion of vaccination errors decreased during the study period and reached 4.1% in 2016 (Fig. 1). Among all medication errors reported in EudraVigilance, 5.5% concerned vaccination errors, ranging from 1.5 to 8.9% per year. In 2012 the number of reports was almost twice as high as in 2011, mainly due to an increase in non-serious reports. After 2012 the proportion of non-serious reports remained high. The majority of cases was received from HCPs (89.9%). In each study year the proportion reported by HCPs was at least 80.0%. The majority of reports received in the study period was spontaneous (95.7%; Table 1). Other report types were reports from study (3.4%; e.g. reports from compassionate use programs, or pharmaco-epidemiological studies), other (0.3%; e.g. when it is not clear from a literature study whether it arose from spontaneous observation or from a study) and in 0.6% of the reports information on the source was not available. The majority of cases originated from the EU (4269; 60.2%; table 1).

Of all reported vaccination errors more than half (59.9%) were serious (table 1) meaning at least one of the following categories was applicable: (1) death, (2) life-threatening, (3) hospitalization, (4) disability, (5) congenital anomaly, or (6) other. The category

[1] MedDRA® is the international medicinal terminology developed under the auspices of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® trademark is owned by IFPMA on behalf of ICH.

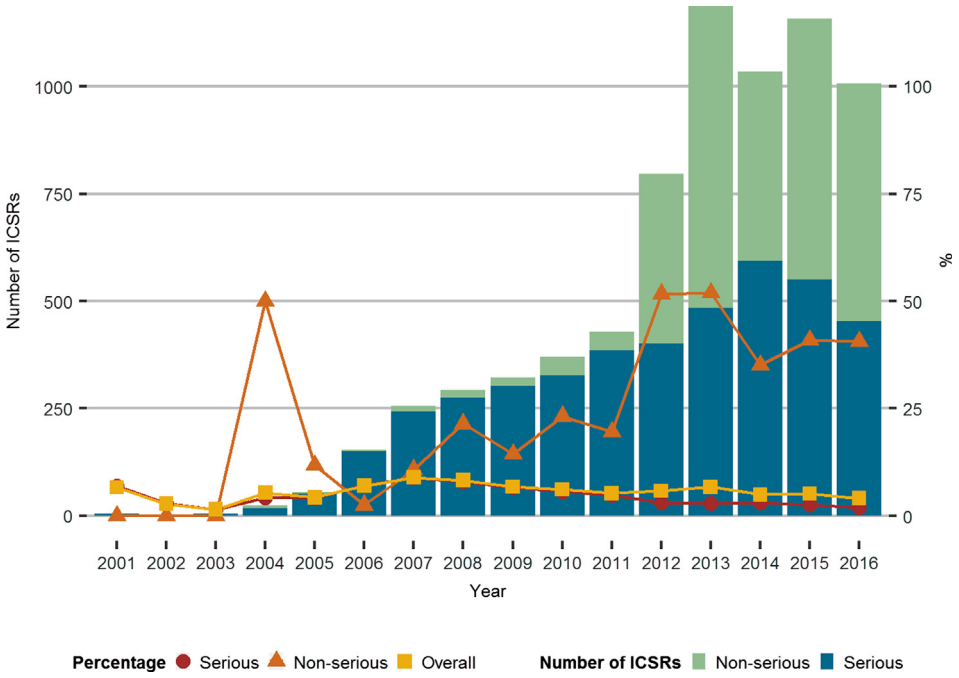

Fig. 1. Number and percentage of vaccination error ICSRs submitted to EudraVigilance per year presented by seriousness of the report. The bars represent the absolute number of serious (blue) and non-serious (green) vaccination errors. The lines represent the percentage of vaccination error cases to the total number of medication error ICSRs submitted in EudraVigilance per year: percentage serious vaccination errors of all serious medication errors (red), percentage non-serious vaccination errors of all non-serious medication errors (orange), percentage vaccination errors of all medication errors (yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Characteristics of vaccination error ICSRs submitted to EudraVigilance between 2001 and 2016.

Variable	*Level*	Total (7097)	<18 years (3023)	≥18 years (2270)
		N (%)	N (%)	N (%)
Gender	*Female*	3913 (55.1)	1468 (48.6)	1875 (67.7)
	Male	2493 (35.1)	1352 (44.7)	817 (29.5)
	Not Specified	691 (9.7)	203 (6.7)	78 (2.8)
Reporter Profession	*Healthcare Professional*	6380 (89.9)	2787 (92.2)	2422 (87.4)
	Non-Healthcare Professional	711 (10.0)	234 (7.7)	346 (12.5)
	Not Specified	6 (0.1)	2 (0.1)	2 (0.1)
Outcome Serious	*Any type*	4248 (59.9)	2029 (67.1)	1721 (62.1)
	Death	187 (2.6)	83 (2.7)	54 (1.9)
	Life threatening	216 (3.0)	94 (3.1)	100 (3.6)
	Hospitalization	1554 (21.9)	858 (28.4)	536 (19.4)
	Disabling	414 (5.8)	110 (3.6)	269 (9.7)
	Congenital anomaly	13 (0.2)	5 (0.2)	5 (0.2)
	Other	2772 (39.1)	1272 (42.1)	1149 (41.5)
Geographic Location	*EU*	4269 (60.2)	1829 (60.5)	1511 (54.5)
	Non-EU	2828 (39.8)	1194 (39.5)	1259 (45.5)
Report Type	*Spontaneous*	6794 (95.7)	2978 (98.5)	2618 (94.5)
	Report from study	239 (3.4)	27 (0.9)	120 (4.3)
	Other	21 (0.3)	4 (0.1)	4 (0.1)
	Not available	43 (0.6)	14 (0.5)	28 (1.0)
Age of Patient	*Mean*	24.1 years	4.68	45.20
	Median	16 years	1	43
	Minimum	0 years	0	18
	Maximum	99 years	17	99
	Standard deviation	24.49 years	5.78	19.00
	Missing	1304	0	0

'other' was reported in two-thirds (65.3%) of all serious cases, followed by 'hospitalisation' (36.6%). Death was reported mostly in the very elderly (≥75 years) compared to the other age categories (13.4% vs 1.7–5.1%; Fig. 2). Disabling outcome was reported more frequently in patients of 12 years and older compared to in infants and children (14.4–18.7% versus 3.4–3.8%). Fig. 4 shows the different proportions of vaccination errors per vaccine for serious and non-serious cases. Fig. 5 shows the distribution of seriousness categories per vaccine.

Reports concerned females significantly more often than males ($p < 0.001$). More than half of the cases were reported in women (55.1%) and males were mentioned in approximately one third of

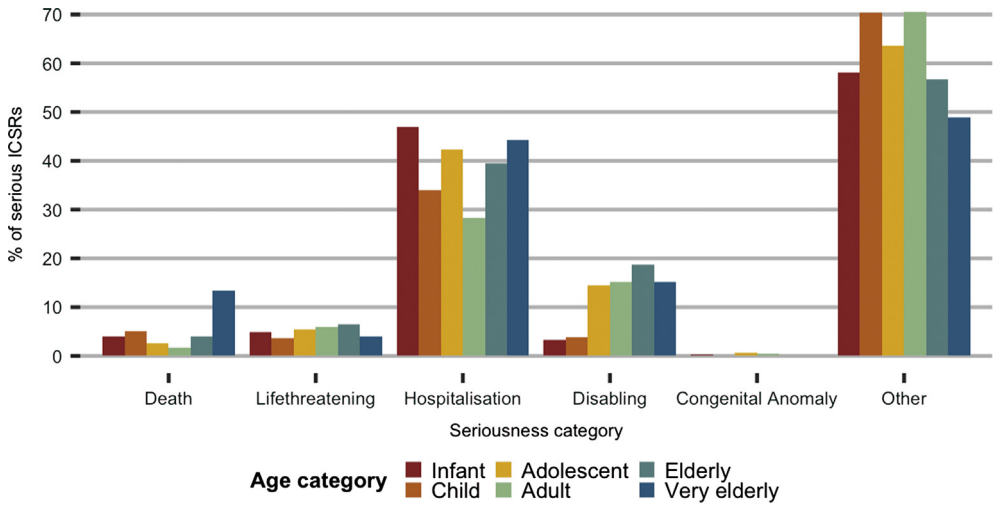

Fig. 2. Percentage of serious categories applicable for vaccination error ICSRs by age category. Percentages are calculated for each age category as the number of ICSRs in the specific seriousness category to the total of serious ICSRs.

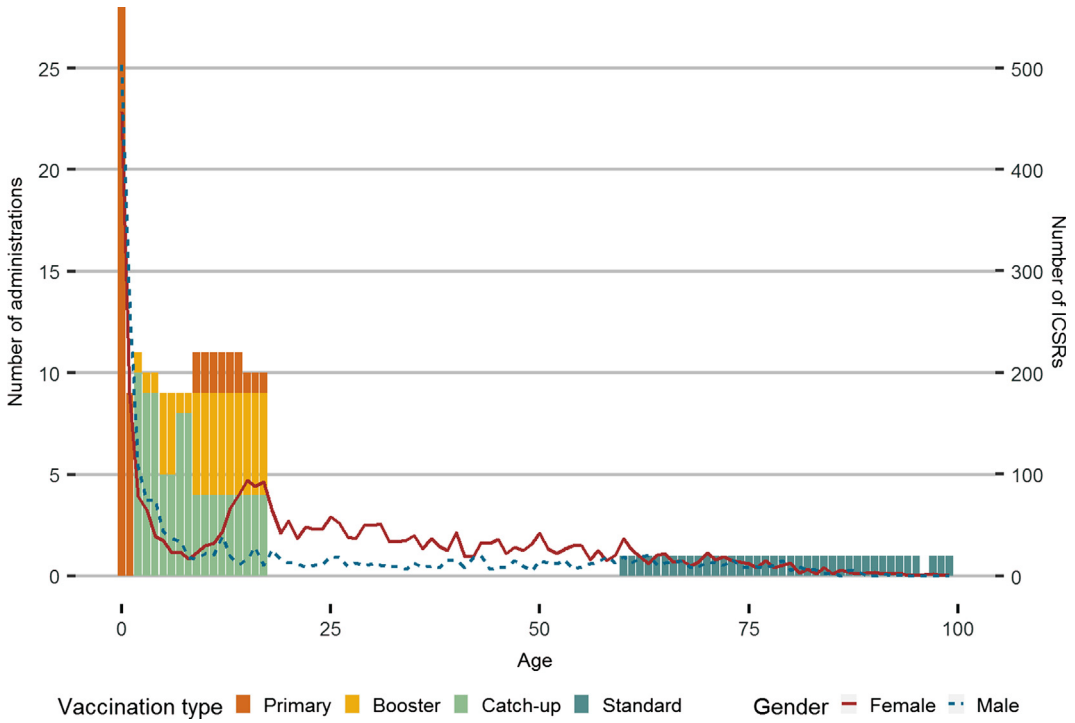

Fig. 3. Number of vaccination error ICSRs received by Age and Gender. The lines represent the number of ICSRs per age and per gender. The bars represent the approximate number of administrations given for each age. The German national immunization schedule was used as a reference for the number of administrations as the majority of ICSRs originated from Germany (Vaccination Schedule Germany. German Standing Committee on Vaccination (STIKO) recommendations, 2017/18. From https://www.rki.de/DE/Content/Infekt/Impfen/Materialien/Downloads-Impfkalender/Impfkalender_Englisch.pdf?__blob=publicationFile. Accessed on 13 July 2018).

the cases (35.1%). In the remaining cases, gender was unknown (9.7%). In total, the ratio of female to male reports was 1.6. The mean age of patients (if provided) was 24.06 years and the median 16. In 18.4% of the cases age was not reported (table 1). Approximately a quarter of all vaccination errors occurred in infants (26.2%). The age distribution was similar in males and females (Fig. 3). However, among adolescents more reports occurred in females. This could be explained by reporting of cases related to papilloma virus vaccines, for which 97.3% of the errors occurred in females. After excluding cases reporting a papilloma virus vaccine the ratio of female to male was still significant ($p < 0.001$) although smaller (1.2).

The majority of adverse events reported after vaccination errors were mild in nature and well known to be associated with vaccine use (e.g. pyrexia, headache and pain in extremity). In table 2 the most frequently reported adverse events are presented for serious and non-serious reports.

Most often reported vaccines were influenza vaccines (957; 13.5%), bacterial and viral vaccines combined (872; 12.3%), and hepatitis vaccines (835; 11.8%). The most frequent bacterial and viral combination vaccines reported were the hexavalent diphtheria-haemophilus influenza B (HiB)-pertussis-poliomyelitis-tetanus-hepatitis B combination (40.8%), followed by diphtheria-pertussis-poliomyelitis-tetanus (27.1%) and diphtheria-HiB-pertussis-poliomye

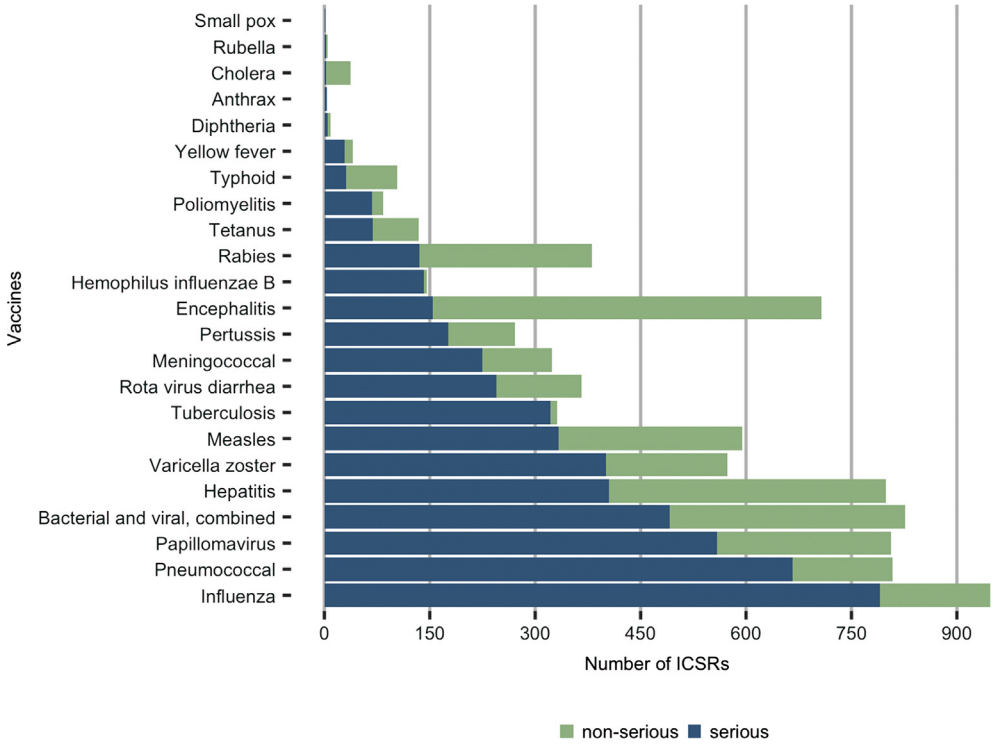

Fig. 4. Number of vaccination error ICSRs by ATC level 5. Data is divided into non-serious ICSRs (green) and serious ICSRs (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

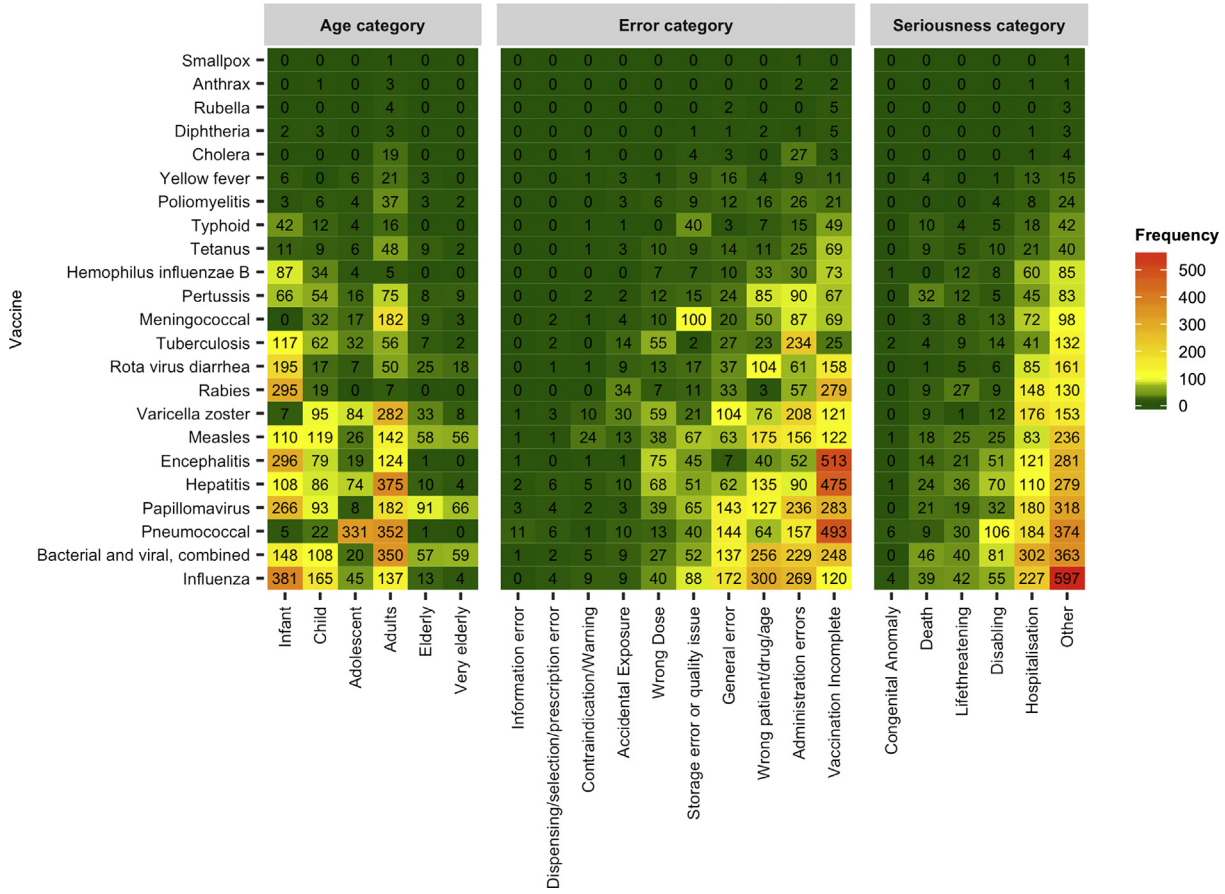

Fig. 5. Number of vaccination error ICSRs by vaccine, age, error category and seriousness category. Each number in the figure corresponds to the absolute number of ICSRs reported for the indicated vaccine and age, error or seriousness category. The vaccines reported most frequently are presented at the bottom of the chart.

Table 2
Adverse events reported in vaccination error Individual Case Safety Reports (ICSRs). Preferred terms included in the narrow Standardised MedDRA Query or the preferred term 'No adverse event' are excluded from this table. Of note: vaccination failure is a term which refers to the failure of the vaccine itself, rather than to an error in the treatment process.

	ADRs overall		Adverse events in serious ICSRs		Adverse events in non-serious ICSRs	
	Adverse event	N (%)	Adverse event	N (%)	Adverse event	N (%)
1	Pyrexia	883 (3.9)	Pyrexia	713 (3.6)	Pyrexia	170 (6.1)
2	Vaccination failure	383 (1.7)	Vaccination failure	317 (1.6)	Syringe issue	93 (3.3)
3	Headache	312 (1.4)	Headache	258 (1.3)	Pain in extremity	74 (2.6)
4	Pain in extremity	293 (1.3)	Vomiting	250 (1.3)	Underdose	69 (2.5)
5	Vomiting	284 (1.3)	Exposure during pregnancy	227 (1.2)	Vaccination failure	66 (2.4)
6	Exposure during pregnancy	252 (1.1)	Pain in extremity	219 (1.1)	Erythema	59 (2.1)
7	Fatigue	235 (1.0)	Pain	204 (1.0)	Vaccination site pain	59 (2.1)
8	Pain	233 (1.0)	Nausea	202 (1.0)	Headache	54 (1.9)
9	Erythema	230 (1.0)	Fatigue	200 (1.0)	Injection site erythema	49 (1.8)
10	Nausea	227 (1.0)	Diarrhoea	176 (0.9)	Overdose	48 (1.7)
11	Malaise	217 (1.0)	Malaise	176 (0.9)	Vaccination site erythema	44 (1.6)
12	Diarrhoea	200 (0.9)	Erythema	171 (0.9)	Off label use	43 (1.5)
13	Asthenia	183 (0.8)	Seizure	169 (0.9)	Malaise	41 (1.5)
14	Dyspnoea	179 (0.8)	Dyspnoea	167 (0.8)	Vaccination site swelling	41 (1.5)
15	Arthralgia	174 (0.8)	Dizziness	158 (0.8)	Injection site pain	39 (1.4)
16	Injection site pain	173 (0.8)	Asthenia	156 (0.8)	Injection site swelling	36 (1.3)
17	Dizziness	171 (0.8)	Arthralgia	150 (0.8)	Fatigue	35 (1.3)
18	Injection site erythema	171 (0.8)	Rash	143 (0.7)	Vomiting	34 (1.2)
19	Seizure	169 (0.8)	Cough	137 (0.7)	Pain	29 (1.0)
20	Rash	160 (0.7)	Varicella	137 (0.7)	Influenza like illness	28 (1.0)

litis-tetanus (16.5%). In infants (0 < 2 years) and children (2 < 12 years) errors in products with bacterial and viral vaccines combined were reported most frequently: 17.8% in infants (of which 60.1% hexavalent vaccine [J07CA09] and 20.7% pentavalent vaccine [J07CA06]) and 16.2% in children (of which 37.1% hexavalent vaccine [J07CA09] and 30.9% a combination vaccine of diphtheria-pertussis-poliomyelitis-tetanus [J07CA02]). In adolescents (12 < 18 years) errors with papilloma virus vaccines were reported most often (47.1%), whereas in adults these were errors with hepatitis virus vaccines (15.2%), and in the elderly and very elderly errors with pneumococcal virus vaccines (27.7% and 28.3%) (Fig. 5).

Within the 7097 cases, a total of 8122 MedDRA PT's associated with medication errors were reported, which were categorized into 10 error groups as per Appendix A. The most frequently reported error group related to non-compliance to the vaccination schedule (36.1%). Most of these cases related to adult patients (48.8%). Secondary to this error category were administration errors (22.1%) and errors relating to a wrong (age of) patient or drug (14.6%) (Fig. 6). The last category was particularly frequent in pediatric patients: 41.9% of these cases were reported in infants (0 < 2 years) and 64.3% in infants and children (<12 years) combined (Fig. 6). Only in infant cases administration errors were reported more frequently than non-compliance issues (29.8%).

The most frequently reported vaccine-error combination was encephalitis vaccine with an error related to non-compliance of the vaccination schedule (5.6%) (Fig. 5). Other vaccines frequently reported with schedule related errors were papilloma (5.3%) and hepatitis vaccines (5.1%). However, when considering age categories, the highest fraction reported was for schedule errors with hepatitis B vaccines in adults. Vaccines frequently reported with administration errors were influenza, tuberculosis and pneumococcal vaccines. Errors with a wrong age of patient, wrong patient or wrong drug were mostly reported with influenza, bacterial and viral combined, and measles vaccines.

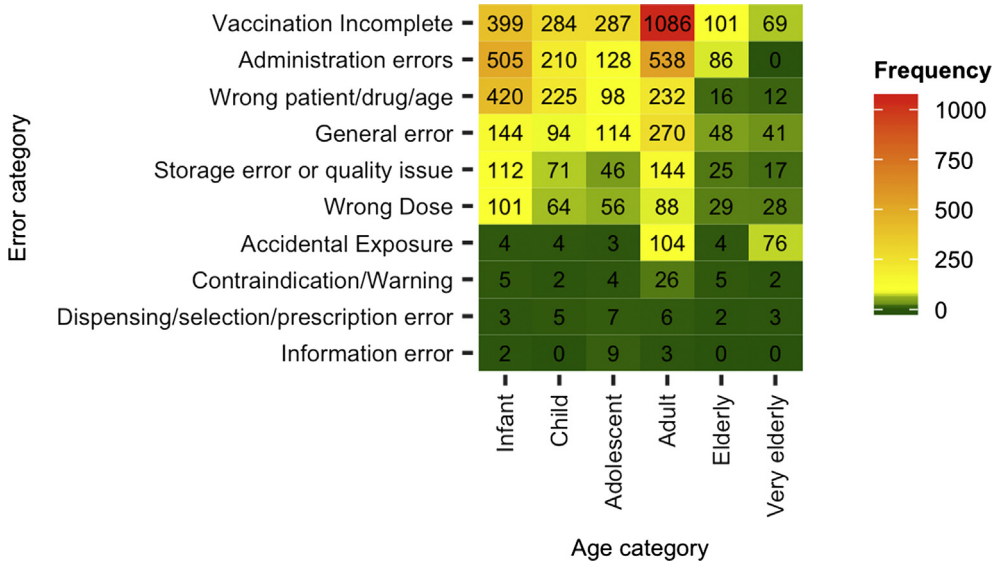

Fig. 6. Number of vaccination error ICSRs by error category and age category. Each number in the figure corresponds to the absolute number of ICSRs reported for the indicated error and age category.

4. Discussion

In our study we present data on vaccination errors identified in the EudraVigilance database. Although several studies have described vaccination errors based on spontaneously reported adverse event reports in the VAERS database [5–12], to our knowledge studies on spontaneous reports of vaccination errors in EudraVigilance are not available.

We observed several key findings:

First, since 2001 we observed a continuous increase of vaccination errors reported to EudraVigilance. This is in line with the US VAERS data for which an increase in vaccination errors was observed during the past decade [12]. It is also in line with the overall observed increase of medication errors in EudraVigilance [4], which could be explained by better infrastructure for spontaneous reporting of adverse events and shifting cultures in healthcare organizations.

Second, there is a change in the ratio of serious and non-serious reports. The vast majority (>75%) of error reports was categorized as serious until 2011, but since 2012 an increase in non-serious reports was observed. The majority of non-serious reports in the EudraVigilance database originated from Germany, and 80% of the German reports was non-serious. The increase in non-serious reports may be driven by the change in the EU pharmacovigilance legislation which was adopted in 2010 (and implemented in 2012). One of the major changes was the obligation for MAHs and NCAs to report not only serious, but also non-serious adverse event reports to EudraVigilance [2]. For the transitional period, however, EU countries could take different approaches for exchange of non-serious adverse events that occurred in the EU. Germany had, as the only member state, specific obligations in place for non-serious reports related to vaccines [21]. This may explain the difference in the serious vs non-serious ratio between Germany and other countries in the EU. With the launch of a new EudraVigilance system in November 2017, the transitional period has ended. Non-serious reports from all EU countries are now collected in EudraVigilance and as a result it is expected that the number of adverse event reports, including vaccination error reports, will increase drastically. For most vaccines, the proportion of serious cases was higher than non-serious cases. Especially tuberculosis vaccines and HiB vaccines concerned almost solely serious cases (both 97.3%).

Third, we also observed a substantial number of fatal cases following vaccination errors. From the current observations, no conclusions can be drawn with regards to causality between the reported errors and fatal outcomes. It may be hypothesized that the relatively small number of fatal outcomes, compared to the large exposure, is due to causes unrelated to vaccines in patients who had only coincidentally received recent immunizations. Additionally, a serious outcome may be more likely to be reported when occurring immediately following immunization even though not caused by it (Silvers 2001). Vaccination errors have the potential to result in very serious outcomes. For example administration of contra-indicated vaccines may result in serious adverse events and have been reported in association with fatal outcomes (Costa 2016). On the other hand, administration of the wrong vaccine, incomplete vaccination or storage errors (with potential to affect the effectiveness of the vaccine) can result in a failure to protect the patient against the intended disease. Failure of immunization may lead to serious disease courses for unprotected patients and potentially to serious outcomes. Although our results show that in general the reported adverse events are mild and also known to be associated with appropriate use of vaccines, serious outcomes or lack of protection of patients do occur in rare cases. It is therefore important to investigate the causality of these serious cases and to identify root-causes of errors, so measures can be taken to prevent future harm. Therefore, the cases of fatal outcomes after errors warrant further research. A manuscript evaluating these cases in depth is in preparation.

Fourth, gender and age are strong determinants: we observed that a large number of vaccination errors were reported in the young pediatric population (<12 years), while for those 12 years and older the number of reported vaccination errors was relatively low, which may be explained by the fact that vaccination schedules often target young children [17,22]. The low observed number of vaccination error reports in the elderly may be explained by the fact that vaccines for the elderly do not require immunization schedules, and usually only one vaccine is administered at a time (e.g. influenza or pneumococcal vaccines) [22]. The gender ratio (excluding papilloma virus vaccines) observed in our data was in line with the gender ratio described for overall adverse event reports in EudraVigilance [23]. The inclusion of human papilloma virus vaccines resulted in a strong increase in the female to male ratio. Women are known to experience/report more adverse events thus the pattern is in line with expectations [24,25].

Since exposure data is not available in EudraVigilance, it is difficult to draw conclusions with regards to the proportion of errors per vaccine. We provided multiple vaccine specific results as it may be useful to focus on vaccine-error combinations, as these may indicate a recurring problem. It was noted that errors related to vaccines which are administered at all ages (such as influenza vaccines) were reported most frequently, whereas errors related to vaccines predominantly administered in infants (such as hexavalent vaccines) were reported more in the youngest age category. When we focus on the type of errors, inappropriate schedule of drug administration was reported most frequently in almost all age categories, which is line with the publication by Hibbs et al on vaccines [12]. Schedule errors with encephalitis, human papilloma virus, and hepatitis vaccines were the most frequently reported error-vaccine combinations. A recent study performed among German paediatric practices showed that indeed adherence to the encephalitis immunization schedule was low, as only 28% of patients who received an initial immunization returned for the second and third injections [26]. Likewise, for HPV vaccination non-completion of the schedule is high [27]. The most frequently reported error-vaccine combination by age category was schedule errors with hepatitis B vaccines in adults. A recent study reported that hepatitis B coverage in the US was suboptimal [28]. The most common reason for non-completion of the two-dose schedule was lack of immunization opportunities [28]. Other reasons for non-completion of an immunization schedule may relate to costs or immunization hesitancy [28]. Several methods have been suggested to reduce schedule errors, such as providing patients with personalized calendars [29], stimulating patients to maintain their immunization history [30] or alerting patients via SMS technology [31]. For infants, administration errors were reported most frequently, of which the majority were related to incorrect route or inappropriate site of drug administration. Frequently reported administration errors were reported due to intramuscular administration of Priorix tetra instead of subcutaneous administration (24%), subcutaneous administration of Prevenar instead of intramuscular administration (13%) and injection of rotavirus vaccines instead of oral administration (13%). Most commonly reported adverse events in these cases were lymphadenitis (41.8% of cases).

5. Limitations

Our study has several limitations. First, EudraVigilance is primarily designed for the collection of spontaneous adverse event reports. While underreporting is a well-known limitation for

spontaneous reporting databases, this may be even more relevant for medication errors as fear of possible consequences or absence of a culture to share and acknowledge errors are known factors that inhibit medication error reporting. With the new legislation (implemented in 2012) the definition of adverse drug reactions has been extended to include medication errors. As a consequence, medication errors that result in harm should also be submitted to EudraVigilance. Due to the nature of spontaneous reports, the numbers in this review should be interpreted with care and serve first of all as a way to identify areas with risk for errors, rather than to quantify these risks. Additionally, in this review, no causality assessment is performed with regards to adverse events or outcomes. All vaccination error cases received by MAHs are discussed routinely in periodic safety update reports to regulatory authorities. All EudraVigilance reports are monitored continuously for new adverse reactions or unexpected outcomes and are in addition, reviewed and discussed in the PSURs. Second, when multiple medications are listed in one report as suspect (or interacting), it is not always clear which of the reported medications was actually involved in the error. As 73% of reports listed only one suspect or interacting medication, it can be assumed that for the majority of reports the vaccine reported was in fact involved in the error. With the implementation of the new ICH-E2B(R3) reporting format in the EudraVigilance system in November 2017, there is the possibility to 'flag' the medication that is related to a medication error [19]. This will support and improve analysis of medication error cases in EudraVigilance. Third, extraction of the dataset was based on the MedDRA SMQN for medication errors. However, more relevant cases may be available in EudraVigilance, as cases where the reporter was not aware of an error are not likely to be coded with one of these terms. Additional search strategies could potentially provide additional cases of vaccination errors. For example, using lot/batch IDs or the product name in combination with the reported patient age could help in identifying cases where a product has been administered to an incorrect age group [32].

6. Conclusion

The number of vaccination errors submitted to EudraVigilance is increasing. It is expected that this number will further increase in the future, especially with the fully functional database launched in November 2017, after which also non-serious cases from the EU should be submitted to EudraVigilance. Vaccination errors vary by age, and the most frequent errors involve inappropriate schedules. As the distribution of error categories followed a similar pattern for all vaccines, it seems that risk minimization does not necessarily need to focus on the vaccine, but rather on the error. For example, clear schedules and reminders for patients may reduce schedule issues, whereas clearer instructions may reduce administration errors, regardless of the vaccine involved. In this study, we analyzed vaccines separately from other medications which may optimize identification of risk factors for vaccination errors that could be lost when analyzed in the large bulk of general medication error reports.

Funding

No sources of funding were used to assist in the preparation of this article.

Conflicts of interest

None of the authors have conflicts of interest that are directly relevant to the content of this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.003.

References

[1] Pharmacovigilance Risk Assessment Committee. Good practice guide on recording, coding, reporting and assessment of medication errors. EMA/762563/2014. Eur Med Agency 2015.
[2] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use., 2010.
[3] Guideline on good pharmacovigilance practices (GVP): Module VI - collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). European Medicines Agency, 2017.
[4] Newbould V, Le Meur S, Goedecke T, Kurz X. Medication errors: a characterisation of spontaneously reported cases in EudraVigilance. Drug Saf 2017;40(12):1241–8.
[5] Varricchio F. Medication errors reported to the vaccine adverse event reporting system (VAERS). Vaccine 2002;20:3049–51.
[6] Woo EJ, Winiecki SK, Arya D, Beeler J. Adverse events after MMR or MMRV vaccine in infants under nine months old. Pediatr Infect Dis J 2016;35(8):e253–7.
[7] Haber P, Moro PL, Cano M, Lewis P, Stewart B, Shimabukuro TT. Post-licensure surveillance of quadrivalent live attenuated influenza vaccine United States, vaccine adverse event reporting system (VAERS), July 2013-June 2014. Vaccine 2015;33(16):1987–92.
[8] Haber P, Moro PL, Cano M, Vellozzi C, Lewis P, Woo EJ, et al. Post-licensure surveillance of trivalent live-attenuated influenza vaccine in children aged 2–18 Years, vaccine adverse event reporting system, United States, July 2005-June 2012. J Pediat Infect Dis Soc 2015;4(3):205–13.
[9] Haber P, Moro PL, McNeil MM, Lewis P, Woo EJ, Hughes H, et al. Post-licensure surveillance of trivalent live attenuated influenza vaccine in adults, United States, vaccine adverse event reporting system (VAERS), July 2005-June 2013. Vaccine 2014;32(48):6499–504.
[10] Haber P, Moro PL, Ng C, Lewis PW, Hibbs B, Schillie SF, et al. Safety of currently licensed hepatitis B surface antigen vaccines in the United States, vaccine adverse event reporting system (VAERS), 2005–2015. Vaccine 2018;36(4):559–64.
[11] Muhammad R, Haber P, Broder K, Leroy Z, Ball R, Braun MM, et al. Adverse events following trivalent inactivated influenza vaccination in children: analysis of the vaccine adverse event reporting system. Pediat Infect Dis J 2011;30(1):e1–8.
[12] Hibbs BF, Moro PL, Lewis P, Miller ER, Shimabukuro TT. Vaccination errors reported to the vaccine adverse event reporting system, (VAERS) United States, 2000–2013. Vaccine 2015;33(28):3171–8.
[13] Haber P, Schembri CP, Lewis P, Hibbs B, Shimabukuro T. Notes from the field: reports of expired live attenuated influenza vaccine being administered — United States, 2007–2014. MMWR 2014;63(35):773.
[14] Caspard H, Wise RP, Steffey A, Brody RS. Incidence of live-attenuated influenza vaccine administration beyond expiry date in children and adolescents aged 2–17 years in the UK: a population-based cohort study. BMJ Open 2017;7(7):e016520.
[15] Shastay A. Administering just the diluent or one of two vaccine components leaves patients unprotected. Home Healthcare Now 2016;34(4):218–20.
[16] Su JR, Miller ER, Duffy J, Baer BM, Cano M. Notes from the field: administration error involving a meningococcal conjugate vaccine — United States, March 1, 2010–September 22, 2015. MMWR Morb Mortal Wkly Rep 2016;19(65):161–2.
[17] Dolan SB, Patel M, Hampton LM, Burnett E, Ehlman DC, Garon J, et al. Administering multiple injectable vaccines during a single visit-summary of findings from the accelerated introduction of inactivated polio vaccine globally. J Infect Dis 2017;216(suppl_1):S152–60.
[18] Vaccine safety basics – learning manual. World Health Organization; 2013; Available from: http://www.who.int/vaccine_safety/initiative/tech_support/Vaccine-safety-E-course-manual.pdf.
[19] Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) – E2B(R3) Data Elements and Message Specification. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2016.
[20] Harmonised Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2a. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1994.
[21] Inspections and Human Medicines Pharmacovigilance Division. Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period, EMA/411742/2015 Rev. 9. European Medicines Agency, 2015.
[22] German vaccination schedule 2017/18. Robert Koch Institut; 2017.
[23] Banovac M, Candore G, Slattery J, Houyez F, Haerry D, Genov G, et al. Patient reporting in the EU: analysis of EudraVigilance data. Drug Saf 2017;40(7):629–45.

[24] Yu Y, Chen J, Li D, Wang L, Wang W, Liu H. Systematic analysis of adverse event reports for sex differences in adverse drug events. Sci Rep 2016;6:24955.
[25] Anderson GD. Chapter 1 gender differences in pharmacological response. Int Rev Neurobiol 2008;83(8):1–10.
[26] Jacob L, Kostev K. Compliance with vaccination against tick-borne encephalitis virus in Germany. Clin Microbiol Inf 2017;23(7):460–3.
[27] Liu G, Kong L, Du P. HPV vaccine completion and dose adherence among commercially insured females aged 9 through 26 years in the US. Papillomavirus Res 2016;2:1–8.
[28] Trantham L, Kurosky SK, Zhang D, Johnson KD. Adherence with and completion of recommended hepatitis vaccination schedules among adults in the United States. Vaccine 2018;36(35):5333–9.
[29] Abbott P, Menzies R, Davison J, Moore L, Wang H. Improving immunisation timeliness in aboriginal children through personalised calendars. BMC Public Health 2013;13:598.
[30] Evans HP, Cooper A, Williams H, Carson-Stevens A. Improving the safety of vaccine delivery. Human Vac Immunother 2016;12(5):1280–1.
[31] Menzies R, McMillan M, Heron L, Lampard J, Joseph T, Chan J, editors. Impact of SMS and calendar reminders on infant immunisation timeliness in Australia. Public health association of Australia communicable diseases control conference; 2017; Melbourne, Australia.
[32] Badoo JA. Review and Analysis of Lot Identifier Information Data in the Vaccine Adverse Event Reporting System (VAERS): Master Thesis Presentation, Hood College, Biomedical Science Regulatory Compliance Program; 2012.